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Efficacy of artisanal preparations of cannabidiol for the treatment of epilepsy: Practical experiences in a tertiary medical center

Giulia S. Porcari [a,1], Cary Fu [b,1], Emily D. Doll [b], Emma G. Carter [b], Robert P. Carson [b,*]

[a] Vanderbilt University School of Medicine, USA
[b] Department of Pediatrics, Monroe Carell Jr. Children's Hospital at Vanderbilt and Vanderbilt University, Nashville, TN, USA

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ABSTRACT

Medically refractory epilepsy continues to be a challenge worldwide, and despite an increasing number of medical therapies, approximately 1 in 3 patients continues to have seizures. Cannabidiol (CBD), one of many constituents of the *Cannabis sativa* or marijuana plant, has received renewed interest in the treatment of epilepsy. While highly purified CBD awaits Food and Drug Administration (FDA) approval, artisanal formulations of CBD are readily available and are seeing increased use in our patient population. Although randomized controlled trials of CBD are ongoing and promising, data regarding artisanal formulations of CBD are minimal and largely anecdotal. Here, we report a retrospective study to define the efficacy of artisanal CBD preparations in children with epilepsy. Given the known interaction between CBD and clobazam, we also conducted a subgroup comparison to determine if clobazam use was related to any beneficial effects of CBD. Additionally, we compared response rates with CBD and with clobazam alone within an overlapping patient cohort. A pediatric cohort with epilepsy of 108 patients was identified through a medical record search for patients using CBD oil. The addition of CBD resulted in 39% of patients having a >50% reduction in seizures, with 10% becoming seizure-free. The responder rate for clobazam was similar. No patients achieved CBD monotherapy, although the weaning of other antiepileptic drugs (AEDs) became possible in 22% of patients. A comparable proportion had AED additions during CBD therapy. With concomitant use of clobazam, 44% of patients had a 50% reduction in seizures upon addition of CBD compared with 33% in the population not taking clobazam; this difference was not statistically significant. The most common reported side effect of CBD was sedation in less than 4% of patients, all of whom were also taking clobazam. Increased alertness and improved verbal interactions were reported in 14% of patients in the CBD group and 8% of patients in the CBD and clobazam group. Benefits were more marked in the CBD alone group, in contrast to the CBD and clobazam group, but this difference was not statistically significant. In summary, these findings support efficacy of artisanal CBD preparations in seizure reduction with few significant side effects. The response to CBD was independent of concurrent clobazam use, although clobazam may contribute to the sedation seen with concurrent CBD use.

1. Introduction

Despite continued development of new medications for the treatment of epilepsy, nearly 1 in 3 patients remain drug-resistant [1,2]. While research into novel treatments of epilepsy is ongoing, we have not yet achieved the goal of "no seizures, no side effects."

In recent years, there has been a resurgence of interest in the use of medical marijuana, or more specifically, cannabidiol (CBD)-containing products in the treatment of medically refractory epilepsy. Greater than 400 distinct chemical entities can be found in *Cannabis s.*, including over 60 cannabinoid compounds [3]. As has been reviewed extensively by others, the pharmacology of individual cannabinoids is complex, with multiple pharmacologic targets independent of the cannabinoid 1 or cannabinoid 2 receptors [4]. As such, a treatment with multiple mechanisms of action may prove to be more effective than that of its constituents in isolation. *Cannabis*-derived products have been used medicinally since at least 2700 BCE by the Chinese and were part of the pharmacopeia in the United States into the 1930s [5].

Excitement regarding the efficacy of CBD in the treatment of epilepsy has grown in large part because of reports of almost miraculous successes by the lay media. While far from being a miracle cure, published

Abbreviations: AED(s), antiepileptic drug(s); CAE/JAE, childhood/juvenile absence epilepsy; CBD, cannabidiol; EME, early myoclonic epilepsy; ESES, electrical status epilepticus of sleep; LGS, Lennox–Gastaut syndrome; THC, tetrahydrocannabinol; TSC, Tuberous Sclerosis Complex; VNS, vagus nerve stimulator.

* Corresponding author at: D-4105 MNC, 1161 21st Avenue South, Nashville, TN 37232-2594, USA.
E-mail address: robert.carson@vanderbilt.edu (R.P. Carson).

[1] GSP and CF contributed equally to manuscript.

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data increasingly suggest that CBD may be efficacious for the treatment of epilepsy. However, concerns for bias remain. A notable study from Colorado, one of the first states to legalize CBD oil for epilepsy treatment, utilized surveys of patient caregivers. The responder rate was reported to be 22% in patients originally from Colorado compared with 47% in patients whose families had moved to the state in order to benefit from CBD oil, a difference which suggests a reporting bias [6]. However, recently published randomized controlled trials of a highly purified pharmaceutical-grade CBD demonstrated efficacy in both Lennox–Gastaut Syndrome (LGS) and Dravet Syndrome, lending support for efficacy in drug-resistant epilepsy [7,8].

In May of 2015, as part of an amendment to TN state law 39-17-402, the State of Tennessee made legal the possession of CBD oil containing less than 0.9% tetrahydrocannabinol (THC) for the treatment of epilepsy. This local legalization has led to a rapid increase in both patient inquiries regarding CBD oil and in the use of CBD-containing products by patients, with and without prior consultation with their physicians. Given the lack of high quality double-blind randomized controlled trials for artisanal CBD preparations, studies which are unlikely to occur, we sought to determine the efficacy of artisanal CBD preparations in our cohort of patients with epilepsy. The hypothesis was that patients with drug-resistant epilepsy would see a reduction in both seizure frequency and in either number or overall dose of standard antiepileptic medications with the addition of CBD-containing products. In addition, given the reported interaction with clobazam, a subgroup analysis was performed comparing response rate of those also taking clobazam with those who were not. Lastly, given the limitations of a retrospective study, we investigated the efficacy of clobazam alone in a similar patient cohort to support the data collection methodology.

In this retrospective study, we report that artisanal CBD is helpful in the treatment of medically refractory seizures.

2. Material and methods

Data were collected in a retrospective manner utilizing the Synthetic Derivative at Vanderbilt University Medical Center from January 2006 through December of 2016. Patients using CBD oil were identified using a keyword search for the terms: “cannabis”, “cannabinoid”, “cannabidiol”, and “CBD oil”. Upon extraction, patient information was deidentified and saved for group analysis upon completion of data collection. The study was approved upon review by the Vanderbilt University Institutional Review Board, IRB#161821.

From within the CBD-searched cohort, a subgroup of patients who use clobazam in addition to CBD as an epilepsy treatment were identified to determine if an interaction between CBD and clobazam contributed to efficacy or side effects (Fig. 1). As validation of the data collection methodology, we identified patients from within the CBD-searched cohort who used clobazam prior to addition of CBD or clobazam alone. This allowed us to assess the clobazam responder rate in a similar cohort of patients. Baseline seizure frequency was determined from the documented seizure frequency most proximal to the introduction of the new agent with responses and side effects derived from clinical documentation in the months following addition of the treatment, often documented in the next clinic visit.

Documented response to CBD or clobazam was organized into 7 categories: seizure-free, >75% seizure reduction, >50% but <75% seizure reduction, <50% seizure reduction or subjective improvement, transient response (better initially, followed by no response/worsening), no benefit, and worsening of seizures. Responders were defined as patients with >50% reduction in seizure frequency. We excluded 6 and 12 patients from the CBD and clobazam groups, respectively, because of inadequate documentation of seizure frequency, treatment response, or to being lost to follow-up.

Numeric results were compared using Student's *t*-test. Categorical data were compared using *z*-test and with logistic regression analysis. Data are presented as mean ± standard deviation (STD) or as number (%).

3. Results

To determine the efficacy of artisanal CBD-containing products in the treatment of medically refractory epilepsy, we utilized the Vanderbilt Synthetic Derivative to identify a total of 329 charts where CBD was documented out of 3,652,459. We identified 210 patients, who were

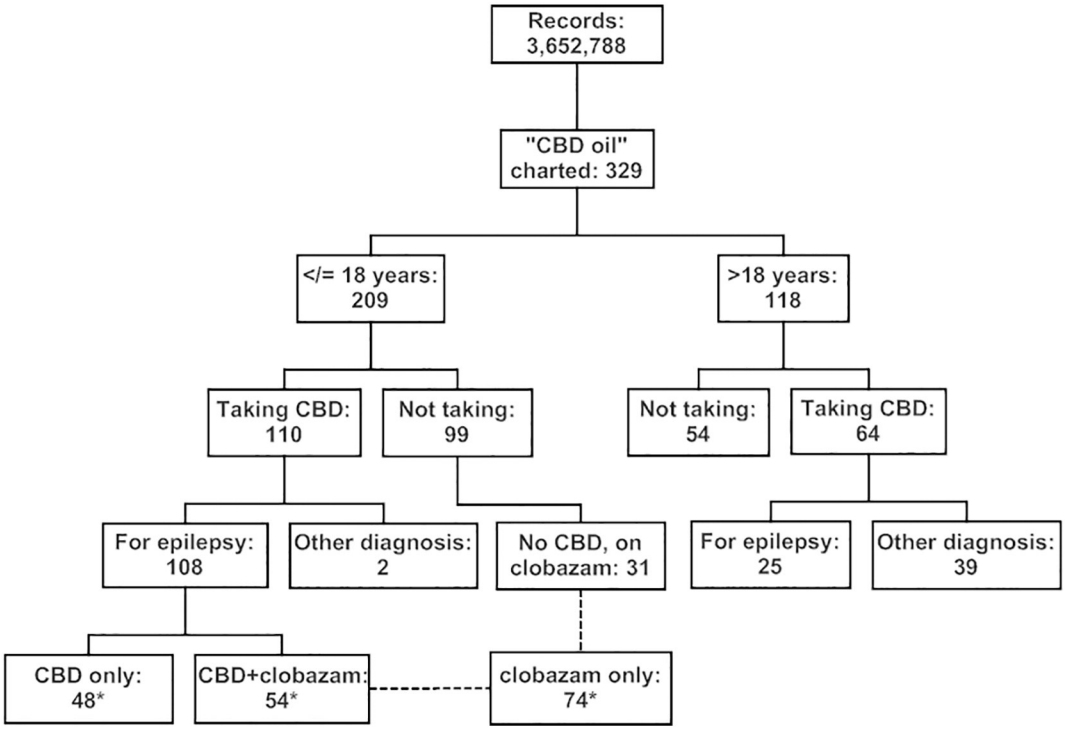

Fig. 1. Patient selection flow diagram. *Notes final number in group following exclusion for inadequate data.

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